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09/503,852	02/15/2000	Jonathan L. Tilly	2653/28	5439

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EXAMINER	
DI NOLA BARON, LILIANA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/503,852	Applicant(s) TILLY ET AL.	
	Examiner Liliana Di Nola-Baron	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18,20-23,27-36 and 46-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-18,20-23,27-36 and 46-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Applicant's amendment, filed on September 29, 2003, is acknowledged.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 4-18, 20-23, 27-36 and 46-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is directed to methods of protecting a female reproductive system against an artificial or natural insult, preserving, enhancing or reviving ovarian function, or preventing or ameliorating menopausal syndromes, comprising administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (ASMase) gene products.

(2) The state of the prior art

The prior art teaches that oocyte apoptosis caused by the chemotherapeutic drug doxorubicin is blocked by sphingosine-1-phosphate (SPP), an ASMase inhibitor. There is no known art wherein a certain composition is administered to successfully prevent menopausal syndrome before its occurrence, preserve or revive ovarian function, or protect the female reproductive system before the occurrence of an insult causing the undesired phenomenon.

(3) The relative skill of those in the art

The relative skill of those in the art having a Ph.D. in the biochemical or microbiological sciences, or having an M.D. is high.

(4) The predictability or unpredictability of the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results from the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by Applicant. Menopausal syndromes, ovarian functions and an undesirable condition in the female

reproductive system can be treated, but cannot be prevented. In the instant application the predictability is very low, since menopausal syndromes, ovarian functions and unwanted conditions in the female reproductive system cannot be prevented, and consequently there is the need for a higher level of directions and guidance by Applicant. However, the amount of direction and guidance provided in the specification is limited to treatment with sphingosine-1-phosphate.

(5) The breadth of the claims

The claims are very broad. No correlation is established between the different artificial insults: chemical, radiation and surgical, nor between the various possible causes of natural insult: genetic background, physiological factors, environmental factors.

(6) The amount of direction or guidance presented

The amount of direction and guidance provided by Applicant is limited. There is no evidence in the specification that established correlation between the different artificial insults claimed by Applicant, nor, with respect to claims 22 and 23, between some of the diseases, for which the artificial insults are used as therapy. With respect to claims 62-80, no correlation has been established in the specification between the various possible causes of natural insult, which Applicant claims: genetic background, physiological factors and environmental factors.

(7) The presence or absence of working examples

The working examples present no data on the effect of the compositions of the invention on the prevention of menopausal syndromes, irregularities in ovarian functions or of an unwanted condition in the female reproductive system

(8) The quantity of experimentation necessary

The effect of the methods of the invention on the different artificial insults, for which no correlation has been established, and which are the result of therapies used for unrelated diseases, and on natural insults, which may be caused by unrelated factors, cannot be predicted a priori, but must be determined from the case to case by painstaking experimental study in vivo. When the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine a possible protecting effect of the methods claimed in the instant application.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 4-18, 20-23, 27-36 and 46-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perez et al. in view of Spiegel and further in view of Igarashi et al.

The claimed invention refers to methods of protecting female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women, comprising administering a composition comprising sphingosine-1-phosphate (SPP).

Perez et al. indicates that conventional cancer therapies, specifically chemotherapy, kill normal cells and one of the most sensitive noncancerous cell type is the ovarian germ cell, and teaches that apoptosis induced by the chemotherapeutic drug doxorubicin is blocked by sphingosine-1-phosphate (See e.g., p. 1228 and Abstract). Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate apoptosis caused by chemical drugs in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231).
Perez et al. does not specify the method and dosage of administration of compositions comprising SPP.

Spiegel provides methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, by administration of sphingosine-1-phosphate and derivatives thereof (See e.g., col. 1, lines 9-17). Spiegel teaches that compositions containing SPP may be administered directly to the cells or parenterally to obtain concentrations of 0.1-100

μM, as well as to the epithelial tissues, such as the rectum and the vagina (See e.g., col. 1, line 46 to col. 2, line 42).

Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically, with suitable doses of sphingosine-1-phosphate depending upon the particular medical application and that the number of doses, daily dosage and course of treatment may vary from individual to individual (See e.g., col. 7, lines 32-65).

Thus, Spiegel and Igarashi et al. provide the teachings that SPP is administered in vivo and disclose a dosage for said administration. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. The expected result would have been successful methods of treatment. Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful. Therefore the invention as a

whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

5. Applicant's arguments filed on September 29, 2003 have been fully considered but they are not persuasive.

6. Applicant argues that apoptosis provides the correlation between the various insults and the invention provides methods of inhibiting such apoptosis. In response to said argument, it is noted that Applicant's invention is not directed to methods of inhibiting apoptosis, but to methods of protecting a female reproductive system, preventing menopausal syndromes and reviving ovarian functions. Even though apoptosis may be a common phenomenon, the diseases claimed by Applicant have different causes and need different treatment. For example, fibroids impair ovarian functions, but are not related to menopausal syndrome.

7. Applicant argues that the correlation between the insults is provided by apoptosis. In reply to said argument, it is noted that natural factors, such as genetic background, physiological factors and environmental factors, as well as artificial factors, such as drugs, act differently and do not necessarily imply apoptosis. If Applicant's invention is directed to a method of treating apoptosis, the claims should clearly read on such a method.

8. In response to Applicant's argument, that there are preventive treatments known in the art, such as vaccines, it is noted that Applicant's invention is not directed to a vaccine. Additionally, even vaccines have limited validity and several shots might be needed. Flue vaccines are good for one season only and do not provide total prevention for life. As for

Applicant's argument, that drugs control blood pressure or cholesterol level, said drugs have a controlling effect, not a preventing effect, and do not prevent heart attacks. Applicant has not provided any guidance in the specification that administration of the drug prevents a disease before its occurrence. Since said guidance is not present in the specification, undue experimentation would be necessary. It is recommended to amend the claims of the instant application to read on methods of treatment, rather than preventing or preserving.

9. Applicant argues that Perez et al. discloses studies, which were performed in vitro and contains specific statements of doubt as to whether the results obtained in vitro can be extrapolated to in vivo treatment of the female reproductive system, and Spiegel and Igarashi et al. are not directed to the field of Applicant's invention. In response to said arguments, it is noted that the statement in Perez et al. that "These data provide a strong impetus for our current efforts to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment" (See p. 1231), strongly suggests to apply the treatment in vivo. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the composition in vivo for the treatment of infertility associated with cancer therapy. The examiner relies on Spiegel and Igarashi et al. for their teachings that SPP is administered in vivo and the disclosure of a dosage for said administration. With respect to the field of Applicant's invention, Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging. Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides the teachings that sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col. 7,

lines32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al., Spiegel and Igarashi et al. to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of the prior art The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

Conclusion

10. Claims 1, 2, 4-18, 20-23, 27-36 and 46-80 are rejected.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

LDN83

December 2, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECH